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The Otherness of Self: Microchimerism in Health and Disease

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Abstract

Microchimerism (Mc) refers to the harboring of a small amount of cells (or DNA) that originated in a different individual. Naturally acquired Mc derives primarily from maternal cells in her progeny, or cells of fetal origin in women. Both maternal and fetal Mc are detected in hematopoietic cells including T and B cells, monocyte/macrophages, NK cells and granulocytes. Mc appears also to generate cells such as myocytes, hepatocytes, islet cells and neurons. Here we examine the detrimental as well as beneficial potential of Mc. The prevalence, diversity and durability of naturally acquired Mc indicates that a shift is needed from the conventional paradigm of “self versus other” to a view of the normal “self” as constitutively chimeric.

Keywords

microchimerism; autoimmune disease; cancer; transplantation; HLA

Naturally acquired microchimerism is common, present within diverse cell types and has functional consequences

In medicine the term chimerism refers to harboring cells or DNA that are genetically disparate, and when in small amounts, the term microchimerism (Mc) is used. It is now well recognized that some cells are exchanged between a woman and fetus during pregnancy [1,2]. Maternal Mc persists into adult life in immune competent healthy individuals [3]. Women who had a birth have Mc of fetal origin many years after childbirth [4]. Miscarriage or induced abortion can produce Mc [5]. Cell transfer between twins can result in Mc [6]. Another likely source of Mc, while not yet reported, is from an older sibling or previous pregnancy of the mother, because the mother could pass cells to the fetus of a subsequent pregnancy.

The recognition that genetically disparate cells are harbored long-term raises the question whether and how these “immigrant cells” impact long-term health. Both maternal and fetal origin Mc have been identified in different cell types and in multiple tissues in humans, sometimes in normal tissues and in a variety of diseases [2,7]. Some approaches to Mc testing are summarized in Text box 1 [2,8,9]. Whether Mc has a beneficial, neutral or adverse effect on the recipient probably depends on a number of factors including the origin

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of the Mc, type of cells acquired, time elapsed since Mc acquisition and age of the recipient. HLA molecules have the potential to impact the balance of good versus bad Mc consequences for the recipient in more than one way and are likely to be key determinants at the interface of “healthy alloimmunity” versus disease, especially for autoimmune disease. Here we summarize current knowledge regarding naturally acquired Mc in health and disease, with emphasis on autoimmune disease and human studies.

Text Box 1

Approaches to identify and characterize Mc

Mc is usually evaluated by testing for either microchimeric DNA or microchimeric cells [reviewed in 2]. In the former approach, DNA is extracted from peripheral blood or tissues and assayed for a genetic polymorphism the test subject does not have. The most common DNA-based approach is testing for male DNA in a female as a marker for presumed prior pregnancy with a male fetus. Maternal Mc can be identified with DNA-based techniques, although the approach is more complex as studies must first be conducted to identify a suitable genetic polymorphism of the mother that the test subject does not have [7].

To evaluate microchimeric cells, fluorescence in situ hybridization (FISH) is most often employed using X- and Y-chromosome specific probes. This approach is suitable for identifying female cells (2 X-signals) in a male (1 X and 1 Y-signal) or male cells in a female. An alternative approach that is not limited to Mc that is sex mismatched, involves targeting other genetic polymorphisms in tissue specimens [8]. A promising technique that was recently reported combines automatic retrieval of single microchimeric cells by laser microdissection and on-chip multiplex PCR for DNA fingerprint analysis [9].

Maternal microchimerism

That maternal Mc can persist into adult life in immunocompetent adults was initially described in peripheral blood [3]. A systematic investigation of maternal Mc in normal human tissues is not available, however, maternal Mc has been detected in apparently normal tissues in the fetus, neonate, children and adults. In second trimester fetuses the thymus, lung, heart, pancreas, liver, spleen, kidney, adrenal gland, ovary, testis and brain had maternal Mc [10]. In newborns and infants who had anomalies, aneuploidy or infection, the thymus, lung, pancreas, liver, thyroid and skin had maternal Mc [11,12]. Maternal Mc was identified in heart and skeletal muscle of some children without and with autoimmune disease [13–15]. The presence of maternal Mc as differentiated organ-specific cells was initially reported in children with the passively acquired autoimmune disease, neonatal lupus; female cardiac myocytes (presumed maternal) were identified in male infants who died from heart block [13]. Differentiated maternal cells in organs have also been found in the absence of autoimmune disease. In the male pancreas, insulin-positive female islet cells, were identified in non-diabetic and diabetic patients [16,17]. Significant quantitative differences of maternal Mc are frequently observed in autoimmune diseases, as discussed below, but it is evident that maternal cells can contribute to the overall body architecture even in healthy individuals.

Maternal Mc has functional consequences in her progeny. T and B cells, natural killer cells, monocyte/macrophages and granulocyte populations contain maternal Mc [18,19]. Interferon gamma was produced when peripheral blood from myositis patients was enriched for maternal cells and then stimulated with the patient's cells [20]. In experimental studies, maternal Mc resulted in production of IL-2 in *IL2* knockout mice [21]. Most lymph nodes of 2nd trimester fetuses contained maternal Mc and when lymph node cultures were depleted of

T regulatory cells (Treg), fetal T cell response to maternal cells increased significantly, indicating fetal Treg-mediated suppression of anti-maternal T cell responses [22]. Moreover, Treg-mediated suppression to maternal, but not paternal alloantigens, was demonstrated up to the age of 17 in some children [22].

Further evidence that maternal Mc has long-term functional consequences comes from transplantation studies. In renal transplantation, sibling grafts had better survival when the recipient's non-inherited maternal HLA antigen (referred to as "NIMA") was present on the sibling donor graft compared to the non-inherited paternal HLA antigen [23]. In a murine model, the percentage of tissues containing maternal Mc correlated with Treg responses measured by maternal-specific suppression of delayed type hypersensitivity and in vivo lymphoproliferation [24]. NIMA-specific pre-transplant immune regulation predicted outcomes of maternal antigen-expressing allograft transplants [25]. While NIMA-specific tolerance has been well described, sensitization can also occur [26,27]. In mice, in utero exposure to NIMA coupled with absence of oral exposure after birth resulted in NIMA-specific sensitization along with loss of maternal Mc [24]. Relative levels of NIMA-specific Tregs versus NIMA-specific T effector cells are likely to influence whether tolerance or sensitization is the outcome. In other experimental studies maternal T cells were identified as the main barrier to in utero hematopoietic cell engraftment [28].

Fetal origin microchimerism

Male Mc (presumed fetal origin Mc) was initially reported in progenitor cells from healthy women who had given birth to sons many years previously [4]. Male Mc was present in almost half of CD34-enriched apheresis products from healthy women donors with unknown pregnancy history [29]. Male DNA was found in mesenchymal cells from bone marrow in all women who had sons in other studies [30]. Systematic evaluation of normal organs for Y-chromosome positive cells by in situ hybridization identified male cells in thyroid, lung, lymph node and skin in women with sons [31] and, in women with and without sons, kidney, liver and heart [32]. Male Mc has been reported in a wide variety of tissues [33–36].

Mc of fetal origin has the potential to differentiate into specific cell types in tissues. Male cells expressing cytokeratin were detected in thyroid, intestine, gallbladder and cervix and expressing a hepatocyte marker in liver in women with multiple diseases (including some autoimmune) [33]. Male cells expressing hepatocyte markers were found in liver specimens from women with sons who had steatosis, hepatitis C and primary biliary cirrhosis [34]. Although it is difficult in human studies to rule out fusion of Mc with recipient cells, in a murine model fetal cell maturation into neurons was demonstrated in the maternal brain and fusion effectively ruled out [37].

Although fetal immune system function has been well-studied, not much is known about the functionality of cells that originated in the fetus but are long-term residents within the maternal environment. In healthy women, male Mc is present within populations of T cells, B cells, monocyte/macrophages, natural killer cells and granulocytes [18,19,38]. The reported cell frequencies are generally low, for example CD3+ T cell concentrations ranged up to 2.7 per 100,000 [18], however, similar frequencies of antigen-specific T cell precursors have been reported [39]. A male T cell clone from a healthy woman produced IFN gamma and IL-4 at low concentrations when stimulated with the woman's HLA antigens and seven male T cell clones from systemic sclerosis patients produced higher levels of IL-4 and lower IFN gamma compared to female T cell clones from the same woman [40]. In a murine model, functional T and B cells of fetal origin have been demonstrated after (and during) pregnancy [41]. Cytotoxic lymphocytes and Tregs specific for male minor antigens are well described in healthy females so it is evident that fetal Mc also has antigenic functional consequences [42].

Fetal origin Mc can be acquired from a miscarriage or induced abortion. Among women without sons, male DNA was found in peripheral blood in almost a quarter who had spontaneous abortions and more than half with induced abortions [5]. In analysis of data from multiple studies an association was observed between male Mc in maternal tissues and maternal history of prior fetal loss [43]. The composition of Mc acquired by women who had induced or spontaneous abortions has not been studied but is likely to differ from pregnancy resulting in a birth because the different fetal cell types and their proportions changes over the course of gestation [44,45]. Genetic anomalies are also more common in spontaneous and induced abortion. During pregnancy, levels of fetal Mc (measured as male DNA), were higher in the blood of women pregnant with trisomy 21 versus normal fetuses [46]. Whether years later similarly high levels are also present is currently unknown.

Naturally acquired Mc and autoimmune disease

The autoimmune disease systemic sclerosis (SSc) has a peak incidence in women in post-reproductive years and has striking clinical similarity to graft-versus-host-disease after hematopoietic cell transplantation, a known condition of chimerism. The primary determinant of graft-versus-host disease is the donor-recipient relationship for HLA genes. Together these observations led to a new area of research investigating Mc and familial HLA relationships in autoimmune diseases [47]. The first report of Mc in an autoimmune disease evaluated fetal origin Mc in SSc and conducted familial HLA-genotyping [48]. Concentrations of male DNA in peripheral blood from women with sons were significantly higher in SSc compared to healthy women with sons. HLA-genotyping of women and children born prior to disease onset revealed increased SSc risk among women who had given birth to an HLA-DRB1 identical or HLA-homozygous child (i.e. HLA-DRB1 indistinguishable from the mother's perspective).

Subsequent studies identified both fetal and maternal origin Mc, in blood and tissues of patients with SSc [7,36,49]. The phenotype of microchimeric cells in SSc tissues is not known, although hematopoietic cell types have been reported in localized scleroderma, a related, but non-systemic disease that often affects children [50]. It is unknown whether or how Mc contributes to SSc pathogenesis. One hypothesis is that microchimeric antigens are presented by patient antigen-presenting cells to patient T cells, referred to as the indirect pathway, a mechanism thought to underlie chronic organ rejection. Multiple sources of Mc as well as trans-generational HLA-relationships are of interest for future study.

Epidemiological, immunogenetic and Mc studies in rheumatoid arthritis (RA) illustrate the potential for beneficial as well as adverse consequences of maternal and fetal origin Mc. The majority of RA patients have HLA class II DRB1 alleles that encode a similar five amino acid motif in the third hypervariable region (QKRAA, QRRRA or RRRRA), referred to as the RA "shared epitope" (SE). Some RA patients, however, do not have the SE. For these individuals there is the possibility risk is conferred when Mc that has the SE is acquired, similar to a "mini-gene transfer." On the other hand, RA genetic studies indicate risk is reduced when HLA-DRB1 alleles encode a different amino acid motif (DERAA), conversely raising the possibility that protection could be conferred if Mc carries the protective motif. Two studies addressed the former possibility by testing for Mc that has the SE in RA patients who lack the SE, both with positive results. The first study provided presumptive evidence of SE-positive Mc, although the SE sequence was not directly measured. The second study identified Mc with specific SE motifs which was detected with increased prevalence and in higher amounts in RA patients compared to controls [51,52].

Similar studies have not yet been done to test for Mc with the RA-protective HLA sequence, but indirect evidence suggests this also occurs. As already discussed, non-inherited maternal

HLA alleles (NIMA) can have long-lasting effects in her progeny. A significant RA-risk reduction was observed when NIMA encoded the RA-protective sequence (compared to the non-inherited paternal HLA allele) [53]. Results have been more variable for studies that asked whether NIMA encoding the SE increases RA risk [reviewed in 54]. However, analyses were generally conducted combining men and women, without considering pregnancy history, and could be confounded because fetal Mc represents another source of Mc encoding either RA-protective or RA-risk sequences.

Epidemiological studies have reported an overall reduction in RA risk for parous compared to nulliparous women (had births vs. no births) [reviewed in 55]. This benefit was found to attenuate with increasing time from delivery [55]. Also, risk was not reduced for women who were gravid (had been pregnant) but not parous (e.g. spontaneous or induced abortion). These epidemiological observations highlight two points. First, while Mc of fetal origin is often referred to as “fetal microchimerism,” the latter term can be misleading, inadvertently conveying the impression that fetal cells acquired by a woman during pregnancy somehow remain “fetal” decades later. Instead, like all cells, it is expected that fetal origin Mc is subject to aging. Second, the composition of cells differs in early versus later fetal life, for example fetal T cells do not appear until 13 weeks gestation [44,45]. Thus cells acquired by the mother are likely to also differ depending on gestational age. One potential explanation for RA-risk reduction in parous but not gravid women and attenuation of benefit over time is acquisition of fetal T cells, educated in the HLA-disparate fetal thymus, and senescence of these cells over time.

Maternal Mc has been examined in the autoimmune diseases myositis, neonatal lupus and type 1 diabetes, and in biliary atresia for which autoimmunity is controversial. In juvenile myositis, maternal Mc was significantly increased in blood and muscle compared to unrelated controls and unaffected siblings [14,15]. In infants who died from neonatal lupus with heart block, maternal cells were found in the myocardium but were infrequent in controls [13]. Phenotypic characterization revealed most of the maternal cells were cardiac myocytes. In children with type 1 diabetes, maternal Mc was detected more often than in healthy children in peripheral blood, and in the pancreas, more insulin positive maternal cells were present in diabetic than non-diabetic pancreases [16,17]. In biliary atresia more maternal CD8+ T cells were found in the liver of patients than controls and some maternal cells were cytokeratin-positive [56]. Mechanisms by which maternal Mc (or fetal Mc) might impact autoimmune disease in her progeny are unknown but some possibilities are summarized in Text box 2 [13–17,20,40,48–55,57].

Text box 2

How Mc might impact autoimmune disease

What role Mc plays in autoimmunity is currently unknown but a number of possibilities have been proposed for different diseases. Maternal T cells were detected in myositis and a role was proposed for maternal Mc as effectors of the immune response [14,15] i.e. “allo-autoimmunity”. In neonatal lupus, maternal cells were identified in affected heart tissues that were cardiac myocytes and the hypothesis proposed that maternal cells are targets of the immune response [13] i.e. “auto-alloimmunity”. In type 1 diabetes, maternal islet cells were detected in the pancreas, in the absence of adjacent inflammatory cells and a role was proposed for Mc in tissue repair and/or regeneration [16,17]. Fetal origin Mc might play a role as effector cells, as antigens presented in the indirect pathway, or in tissue repair and/or regeneration [41, 48 and reviewed in 2]. Maternal Mc could also impact autoimmunity in her progeny by influencing the fetal response towards self-antigens in utero [57].

Fetal origin Mc has been examined in systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), primary biliary cirrhosis (PBC), autoimmune thyroid disease (AITD) and multiple sclerosis (MS). In SLE renal biopsies of female patients with nephritis had significantly more male cells than controls [58]. Other reports for SLE have been variable, some finding a difference in patients compared to controls and others not [reviewed in 59]. In SS, labial salivary glands contained Mc when patients had secondary SS coexisting with SSc but not in patients with primary SS [60]. PBC has a marked female predilection and pathologically resemblances graft-versus-host disease of the liver. Most studies of liver specimens failed to find a significant difference of Mc in PBC patients compared to controls [reviewed in 61], not because male DNA was infrequent in PBC, but rather because Mc was also frequent in other types of liver disease. It remains possible, however, that the type of Mc, whether from a birth, miscarriage or induced abortion or Mc from daughters could be a variable in PBC. AITD has a marked female predilection and especially high incidence postpartum. An increased frequency of male Mc in thyroid tissue has been described in Hashimoto's and Graves disease although Mc has also been observed in some non-autoimmune thyroid conditions [reviewed in 2,62]. In MS, Mc was investigated in monozygotic and dizygotic twins concordant and discordant for MS [63]. Mc was increased in affected females from monozygotic concordant pairs compared to monozygotic discordant pairs that were affected and unaffected and the overall rate of Mc was significantly higher in affected twins than unaffected co-twins. Mc was thought to be mostly from offspring, with a few possibly from a twin or the mother.

HLA molecules at the interface of “healthy alloimmunity” and autoimmunity

HLA molecules play a central role in immune responses and are also key determinants of iatrogenic chimerism in graft rejection and graft-versus-host disease in transplantation. Mothers and their offspring share one HLA haplotype and most often differ for their other haplotype and HLA alleles because HLA genes are highly polymorphic. However, sometimes a mother and child have similar HLA alleles on their non-shared HLA-haplotype as illustrated in Figure 1A.

A few studies have evaluated Mc according to HLA-relationships. Blood obtained by cordocentesis (median age 26 weeks) was assayed for maternal Mc and HLA-genotyping conducted for mother-fetus pairs. Both the frequency and concentration of maternal Mc was higher when there was maternal compatibility for HLA-DQB1 from the perspective of the fetus i.e. the mother was DQB1 homozygous or HLA-identical [64]. In a mouse model that evaluated maternal-fetal major histocompatibility complex (MHC) relationships for the entire haplotype (all MHC class I and class II), maternal Mc concentration in tissues (lymphoid and brain) were higher when the progeny was homozygous than heterozygous [65]. While results of these two studies contrast they are not comparable with each other as the latter study is of inbred mice that had MHC sharing for an entire haplotype (class I and II) and tested tissues in contrast to the former study of humans that tested blood. In other murine studies Treg responses to maternal alloantigens correlated with maternal Mc levels in multiple organs [24].

Whether HLA-compatibility impacts the prevalence, amount, or type of fetal origin Mc in women has not been specifically addressed in humans. The amount of fetal origin Mc detected in peripheral blood of women with SSc was higher than in healthy women and SSc risk was increased for women who had given birth to an HLA-DRB1 compatible child, however different inclusion criteria for the two sets of studies in this report precluded analysis for correlation [48]. Mice mated syngeneically were more likely to develop persistent fetal Mc than those mated allogeneically [66].

Because both maternal and fetal cells become long-term residents it will be of interest to evaluate HLA-relationships across generations in women. As illustrated in Figure 1B, families sometimes exhibit HLA-sharing across generations. This can occur, for example, when a child's paternally-inherited HLA allele is the same as the grandmother's HLA allele that was not inherited by the mother (NIMA) [Column 2 of Figure 1B]. Another question for future studies is whether maternal Mc and fetal origin Mc carry equal weight, or whether the latter is trump, for example when it encodes an RA-protective allele but the NIMA encodes an RA risk allele.

Multi-Generational Mc and other sources of Mc

In addition to maternal Mc, females can acquire multi-generational Mc due to their own pregnancies. Transgenerational Mc is of immunologic interest especially because maternal Mc is acquired while the immune system is developing whereas fetal origin Mc is acquired to a mature immune system. As discussed above, a grandchild could inherit the same HLA allele as the non-transmitted grandmaternal HLA allele but whether this type of familial HLA-relationship has consequences for a woman has not been examined. Another question is whether multiple sources of Mc compete or are additive within an individual. Healthy women with greater parity had a significant reduction of maternal Mc in peripheral blood suggesting competition occurs between fetal and maternal "grafts" [67].

More than one Mc source can also be harbored by males, children and never pregnant females, because Mc can be acquired from a twin Mc [6] or potentially from an older sibling or prior pregnancy of the mother. The latter is supported by a study in which male cells were found in female fetuses [68]. This study also indicates male DNA in an adult female does not always derive from prior pregnancy with a male fetus. Another Mc source is blood transfusion. Blood products are generally irradiated before administration to immune compromised individuals, but non-irradiated transfusions, particularly in multiply transfused trauma patients, can result in long-term engraftment [69].

Mc in cancer and in response to injury

Donor HLA disparity increases graft-versus-host disease risk in the transplantation setting [70], however, it is now known that benefit also accrues because risk of recurrent malignancy is reduced [71]. A graft-versus-tumor effect has been described for leukemia and for solid tumors [71]. These observations, by analogy, raise the question whether naturally acquired semi-allogeneic Mc can impart benefit against development of malignancy in the recipient. Fetal origin Mc was initially investigated in breast cancer, based on transplantation observations and because breast cancer is reduced in parous compared to nulliparous women (with vs. without births). Supporting this concept, male DNA, presumed fetal origin Mc, was less prevalent in peripheral blood of women with breast cancer than healthy women [72].

Fetal origin Mc has also been investigated in thyroid cancer, cervical cancer, lung cancer and melanoma [73–81]. The usual approach has been to test for male DNA or male cells in female patients. In women with papillary thyroid cancer, the prevalence of male DNA was reduced in peripheral blood compared to healthy women [73], similar to observations in breast cancer. In most studies of cancer the proposed role of fetal origin Mc has been beneficial, with a suggested role in tissue repair, repopulation and/or immune surveillance. However, a role in disease progression has also been considered as contributing to lymphangiogenesis or tumor growth, for example in melanoma [80].

A graft-versus leukemia effect was recently described in patients with acute myeloid or lymphoblastic leukemia undergoing cord blood transplantation. Although, the evidence is

indirect, the results strongly implicate that maternal Mc in the transplanted cord blood samples is associated with decreased chance of relapse following transplantation [82]. Conversely, an important question for future studies is whether Mc of any type is sometimes the origin of a malignancy. Many years ago, maternal to fetus lymphocyte transfer was proposed to underlie some cases of Hodgkin's disease [83].

It is difficult in human studies to discern the role of Mc that is present in tissues, especially Mc in normal tissues [31–33]. However, experiments in mice support the concept that Mc can contribute to tissue repair. Fetal cell migration to injured liver, brain and heart have all been described in murine models [37,84,85]. Moreover, differentiation of fetal cells has also been demonstrated including into neurons [37] as well as different cardiac lineages [85]. A role in repair has also been suggested in non-autoimmune inflammatory diseases [86].

Concluding remarks

To date, most Mc investigations have focused on autoimmune diseases or cancer while concomitantly establishing baseline information for healthy individuals. The initial Mc studies evaluated diseases where an adverse role was hypothesized, however, the potential for benefit has also been apparent, even in autoimmunity. In diseases such as RA, Mc could provide benefit or risk, according to the specificity of the acquired Mc. Maternal Mc has been implicated in myositis and neonatal lupus in an adverse role, but as potentially beneficial in other diseases such as type 1 diabetes. A positive contribution of fetal origin Mc has been explored in diseases such as breast cancer, for which parity is protective, whereas a negative contribution has been suggested for other forms of cancer such as melanoma. An outstanding question is whether microchimeric cells, like other cells, can undergo malignant transformation in the recipient. This merits exploration as does asking whether aging maternal Mc within us presents any risk, as even if transformation occurs rarely or not at all, insight might be gained into how malignancy is averted.

Naturally acquired Mc has also been studied in complications of pregnancy, infection and transplantation. Relatively unexplored areas include cardiovascular disease, degenerative diseases, and for maternal Mc, a potential role in normal development. A question of particular interest for degenerative disease is whether accumulation of abnormal fetal origin Mc is responsible for the increased risk of Alzheimer's disease with increasing number of pregnancies [87] and the five-fold increased risk of Alzheimer's in mothers who gave birth to a child with trisomy 21 [88]. Fetal origin Mc has not been reported in human brain, but has been described in maternal mouse brain [37]. Some important questions are whether Mc from spontaneous and/or induced abortion affects long-term maternal health and how women are protected from harboring Mc from a genetically abnormal fetus long-term. Epidemiological observations of disease risk according to parity, gravidity and birth order, reveal clues for further investigation, birth order because sibling Mc probably occurs and could be to the benefit or at a cost for a later born child.

The recognition of naturally acquired Mc as a part of normal biology, including contribution to circulating and tissue-specific cells contrasts with the classical paradigm in which health is assumed to reside in separateness of "self" and "other". Although this area of research in humans is relatively new, chimerism is well described in other organisms and in evolution [89]. While much is unknown about naturally acquired Mc in humans it is apparent these immigrant cells are with us for the long-term. Perhaps the human placenta is less a barrier than a selective immigration policy evoking the expression "*E pluribus unum*", out of many, one.

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Figure 1.

The four types of HLA-relationships of a mother and child are illustrated in Figure 1A. In the example, in column 1 there is bi-directional HLA incompatibility. In column 2 the child is HLA-identical to the mother resulting in bi-directional HLA compatibility. In column 3 the child inherited the same HLA allele from the father as the mother (homozygosity), which results in uni-directionally compatibility from the mother's perspective with incompatibility from the child's perspective. Similarly if the mother is homozygous the reverse is true (column 4). HLA-compatibility that results from HLA-identity or HLA-homozygosity has been hypothesized to contribute to some autoimmune diseases in which Mc is implicated [2,48]. Women can acquire Mc from their mother and from the fetus during their own reproductive life, thus becoming a recipient to Mc across generations. Although most of the time these different sources of Mc will differ for HLA alleles, the child's paternally-inherited HLA allele could be the same as the HLA allele that was not transmitted from the grandmother to the child's mother as illustrated in Figure 1B, column 2. Whether these types of familial HLA-relationships could predispose to autoimmunity is currently not known but is a subject of interest for future studies.

Organ	Presumed Cell Type	Maternal origin MC	Fetal origin MC
Brain	Neurons		X
Lymph node	Hematopoietic cells (CD45)		X
Thyroid	Epithelial cells, thyroid cells		X
Blood	T cells, B cells, monocytes/macrophages, NK cells, granulocytes	X	X
Blood	Lymphoid progenitor cells		X
Heart	Cardiac myocytes	X	X
Skin	Endothelial cells		X
Skin	Keratinocytes	X	
Spleen	Hematopoietic cells (CD45)		X
Kidney	Renal tubular cells	X	
Pancreas	Islet beta cells	X	
Liver	Hepatocytes	X	X
Gallbladder	Epithelial cells		X
Intestine	Epithelial cells		X
Cervix	Epithelial cells		X

Figure 2.

Naturally-acquired Mc has been identified in organs as multiple different types of differentiated cells and within a variety of hematopoietic cell lineages in humans. Maternal Mc and fetal origin Mc in women are the most common Mc sources. Hematopoietic Mc is found in individuals who are otherwise healthy, and differentiated cells in tissues have also been described in the absence of disease. These observations indicate naturally acquired Mc is likely an integral aspect of “the self,” with lifetime consequences sometimes for better and others times for worse.